Errata to FDA Background Package
Psychopharmacologic Drugs Advisory Committee
December 12, 2011

Errata 1
Briefing Package
Clinical Review
Page 7 (Page 16 of PDF), Paragraph #6

Original text
"…commercial version of the inhaler (used in some of the earlier trials) compared to the clinical version (used in the efficacy trials and planned for marketing"

Amended text
"…commercial version of the inhaler (used in the later trials and planned for marketing) compared to the clinical version (used in the efficacy trials)"

Errata 2
Briefing Package
Clinical Review
Page 13 (Page 22 of PDF), Paragraph #1

Original text
"…In the trials of healthy volunteers (**004-101**, **004-102**, **004-103**, **004-104**, and **004-107**), subjects who reported regular tobacco use within the last year were excluded. The only exception was in Trial **004-106**, a pharmacokinetic study of healthy smokers compared to nonsmokers, but in this trial subjects were excluded for FEV_1 < 80% of predicted or FVC < 80% of predicted."

Amended text
"…In the trials of healthy volunteers (**004-101**, **004-103**, **004-104**, and **004-107**), subjects who reported regular tobacco use within the last year were excluded. The only exceptions were in Trial **004-102**, in which subjects with a history of asthma or chronic obstructive lung disease were excluded, and in Trial **004-106**, a pharmacokinetic study of healthy smokers compared to nonsmokers, but in this trial subjects were excluded for FEV_1 < 80% of predicted or FVC < 80% of predicted."

Errata 3
Briefing Package
Clinical Review
Page 14 (Page 23 of PDF), Paragraph #5

Original text
"…excluding subjects with clinically significant pulmonary disease from the pivotal trials and subjects who reported regular tobacco use from the Phase 1 and Phase 2 trials

resulted than a better pulmonary safety profile than would be expected in the target population."

Amended text
"…excluding subjects with clinically significant pulmonary disease from the efficacy trials (004-201, 004-301, and 004-302) and subjects who reported regular tobacco use from many of the Phase 1 trials resulted than a better pulmonary safety profile than would be expected in the target population."

Errata 4
Briefing Package
Clinical Review
Page 32 (Page 41 of PDF), Last Paragraph (Reviewer's Comments)

Original text
On my review of the listing, 50 subjects (not 52) were listed as having asthma or COPD (three subjects were listed as having both asthma and COPD, so two of the three may have been counted twice). Of the 50 asthma and COPD subjects, 6 had childhood asthma, 1 was reported to have mild asthma (no current symptoms), 1 had asthma not clinically significant or clinically apparent, 1 had asthma not clinically apparent, 1 had history of asthma (not clinically apparent), 1 had asthma 1971, 1 had asthma (8/2006), 1 had asthma (1993), 1 had asthma – UNK-1978 – UNK 1992, and 1 had asthma – no symptoms in many years. Of the remaining patients with asthma or COPD, 6 had asthma (or history of asthma) which was described as resolved. The remaining 29 subjects had asthma or COPD described as stable. Eleven of these 29 patients received placebo, leaving 18 subjects with stable asthma or COPD who received Staccato Loxapine.

Amended text
On my review of the listing, 52 subjects were listed as having asthma or COPD (three subjects were listed as having both asthma and COPD). Of the 52 asthma and COPD subjects, 6 had childhood asthma, 1 was reported to have mild asthma (no current symptoms), 1 had asthma not clinically significant or clinically apparent, 1 had asthma not clinically apparent, 1 had history of asthma (not clinically apparent), 1 had asthma 1971, 1 had asthma (8/2006), 1 had asthma (1993), 1 had asthma – UNK-1978 – UNK 1992, and 1 had asthma – no symptoms in many years. Of the remaining patients with asthma or COPD (includes one patient with chronic bronchitis), 6 had asthma (or history of asthma) which was described as resolved. The remaining 31 subjects had asthma or COPD described as stable. Twelve of these 31 patients received placebo, leaving 19 subjects with stable asthma or COPD who received Staccato Loxapine.

Errata 5 and Errata 6
Briefing Package
Pulmonary Review
Page 12 (Page 112 of PDF), Paragraph #2

Original Text

In these 3 trials, there were 4 patients (7.6%) with airway related adverse events in the combined loxapine groups, compared to none in placebo. Two patients in the loxapine 5

mcg dose group had wheezing and one patient in the loxapine 10 mcg group had cough, all of which resolved without treatment. One patient in the loxapine 10 mcg group was discontinued from the trial due to bronchospasm.

Amended Text

In these 3 trials, there were 4 patients (0.8%) with airway related adverse events in the combined loxapine groups, compared to none in placebo. Two patients in the loxapine 5 mg dose group had wheezing and one patient in the loxapine 10 mg group had cough, all of which resolved without treatment. One patient in the loxapine 10 mg group was discontinued from the trial due to bronchospasm.

Errata 7
Briefing Package
Pulmonary Review
Page 13 (Page 113 of PDF), Paragraph #3

Original Text

- Patients with acute agitation may be unable to give a reliable history of airway disease and be uncooperative with physical examination, making screening these patients out prior to administration difficult. In the Phase 2 and 3 clinical trials, patients with clinically apparent asthma and COPD were ineligible for the trial and were screened in an unagitated state two weeks prior to enrollment. Even so, four patients had clinical symptoms of bronchospasm, and one was discontinued due to acute wheezing that required albuterol.

Amended Text

- Patients with acute agitation may be unable to give a reliable history of airway disease and be uncooperative with physical examination, making screening these patients out prior to administration difficult. In the Phase 2 and 3 clinical trials, patients with clinically apparent asthma and COPD were ineligible for the trial and were screened up to two weeks prior to enrollment for schizophrenia patients and up to 24 hours prior to enrollment for bipolar patients. Patients were not necessarily in an agitated state during screening. Even so, four patients had clinical symptoms of bronchospasm, and one was discontinued due to acute wheezing that required albuterol.

Errata 8
Briefing Package
Pulmonary Review
Page 14 (Page 114 of PDF), Paragraph #2

Original Text

- The proposed dosing for inhaled loxapine is every 2 hours for up to three 10 mg doses. No spirometry safety data are available at this dosing frequency or number of doses. Pulmonary safety trials in asthma and COPD patients were performed

with dosing every 10 hours for 2 doses, and there was evidence of worsened airflow obstruction after the second dose. Further, in the asthma trial, FEV1 did not return to baseline as late as 14 hours after the second dose, increasing the risk of severely worsened lung function if an additional dose were given prior to recovery.

Amended Text

- The proposed dosing for inhaled loxapine is as frequently as every 2 hours for up to three 10 mg doses. No spirometry safety data are available at this dosing frequency or number of doses. Pulmonary safety trials in asthma and COPD patients were performed with dosing every 10 hours for 2 doses, and there was evidence of worsened airflow obstruction after the second dose. Further, in the asthma trial, FEV1 did not return to baseline as late as 14 hours after the second dose, increasing the risk of severely worsened lung function if an additional dose were given prior to recovery.

Errata 9
Briefing Package
Pulmonary Review
Page 36 (Page 136 of the PDF), Paragraph #1

Original Text

Looking over the course of the study, the largest change from baseline in a placebo treated subject was -40% associated with an AE of bronchospasm. The largest change in a loxapine treated subject was -46.1%, which was not associated with any airway AE.

Amended Text

text deleted as the data are from the COPD study

Errata 10 and Errata 11
Briefing Package
Pulmonary Review
Page 43 (Page 143 of PDF), Last Paragraph

Original Text

It is even more concerning that the decrease was markedly larger and did not show recovery after the second dose, which was given 8 hours after the first dose. The proposed dosing interval for Staccato Loxapine is every 2 hours up to 3 times per day, which would imply repeat dosing prior to FEV1 recovery.

Amended Text

It is even more concerning that the decrease was markedly larger and did not show recovery after the second dose, which was given 10 hours after the first dose. The proposed dosing interval for Staccato Loxapine is as frequently as every 2 hours up to 3 times per day, which would imply repeat dosing prior to FEV1 recovery.

Errata 12
Briefing Package
Pulmonary Review
Page 54 (Page 154 of PDF), Paragraph #2

Original Text

Since patients who received rescue medication were excluded from the analysis of oxygen levels, the occurrence of hypoxia was not adequately evaluated in this trial and remains a concern for patients treated with Staccato Loxapine.

Amended Text

Patients who received rescue medication were excluded from the analysis of oxygen levels. Because rescue medication may have affected oxygen saturation, the true occurrence of hypoxia could not be evaluated in this trial and remains a concern for patients treated with Staccato Loxapine.

Errata 13
Briefing Package
Division of Risk Management (DRISK) Review
Page 2 (Page 179 of PDF), Paragraph #2

Original Text
"…a risk mitigation strategy (beyond labeling) is likely to be required to address the risk of asthma-related death."

Amended Text
"…a risk mitigation strategy (beyond labeling) is likely to be required to address the risk of serious patient outcomes that could result from post-administration bronchospasm associated with loxapine inhalation powder."